Pharmacology

Drugs that Affect the Cardiovascular System

Topics

- Electrophysiology
- Vaughn-Williams classification
- Antihypertensives
- Hemostatic agents

Cardiac Function

- Dependent upon
  - Adequate amounts of ATP
  - Adequate amounts of Ca^{++}
  - Coordinated electrical stimulus

Adequate Amounts of ATP

- Needed to:
  - Maintain electrochemical gradients
  - Propagate action potentials
  - Power muscle contraction

Adequate Amounts of Calcium

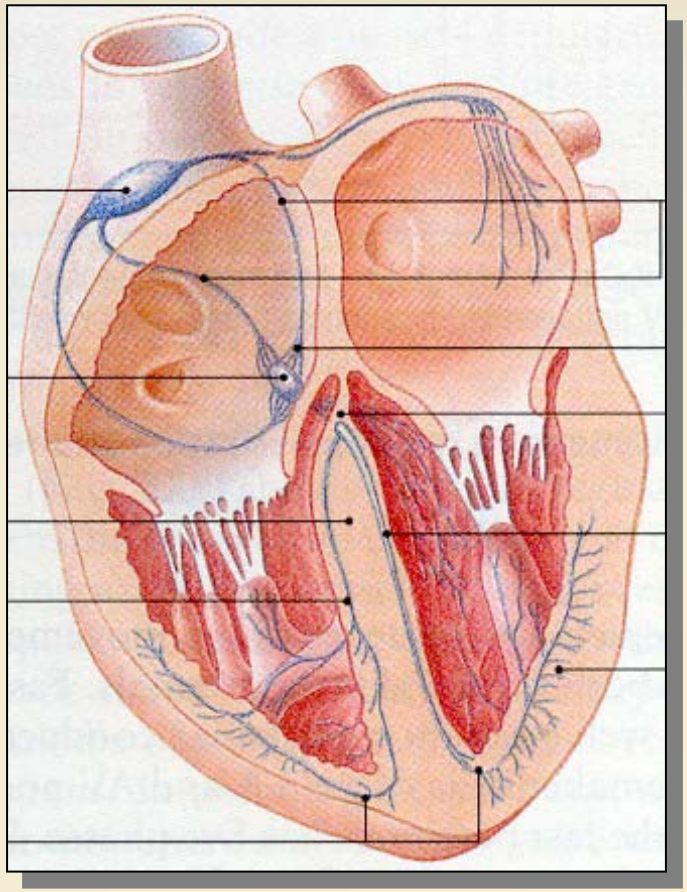
- Calcium is ‘glue’ that links electrical and mechanical events.

Coordinated Electrical Stimulation

- Heart capable of automaticity
- Two types of myocardial tissue
  - Contractile
  - Conductive
- Impulses travel through ‘action potential superhighway’.

A.P. SuperHighway

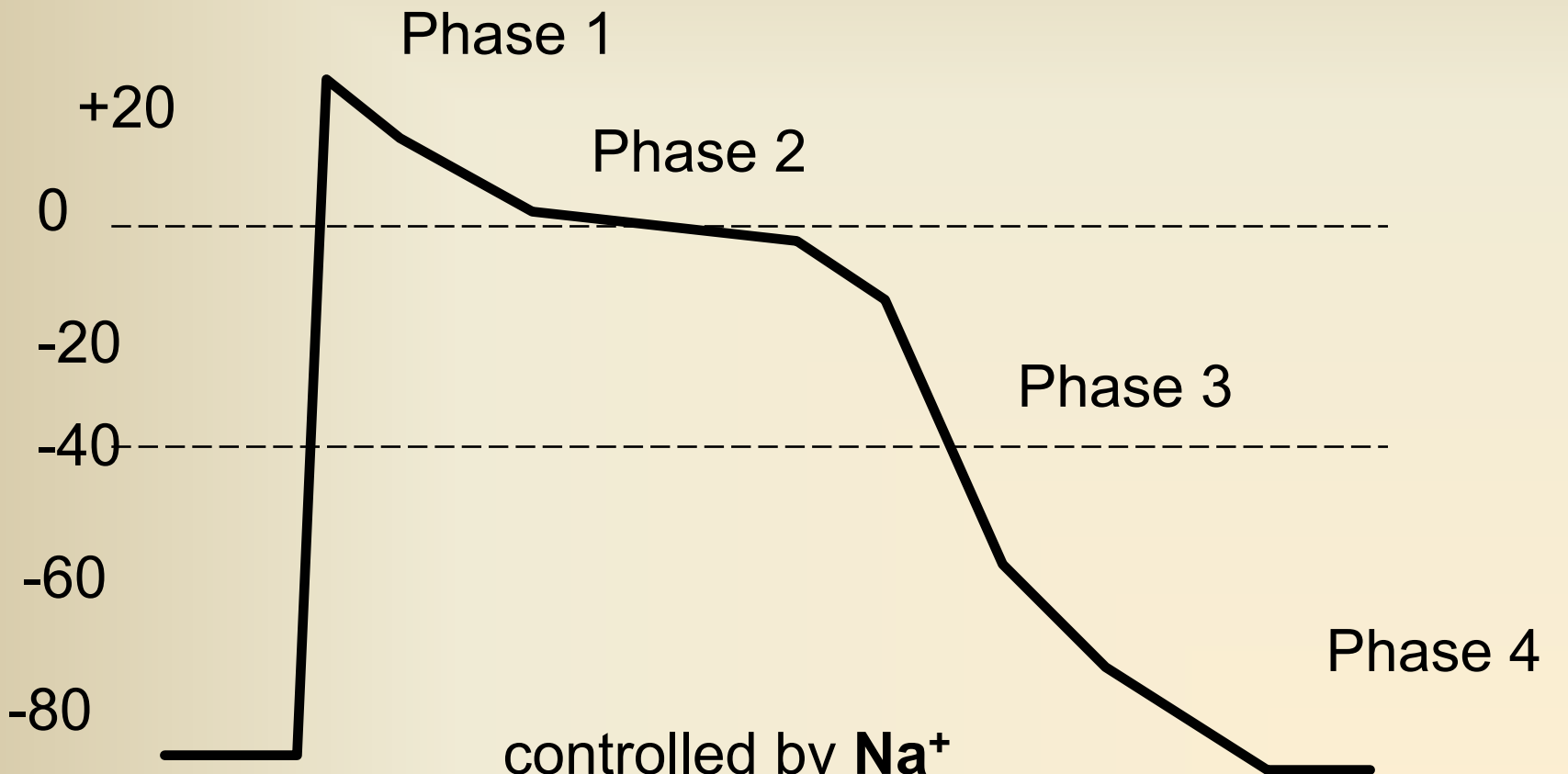
- Sinoatrial node
- Atrioventricular node
- Bundle of His
- Bundle Branches
  - Fascicles
- Purkinje Network



Electrophysiology

- Two types of action potentials
  - Fast potentials
    - Found in contractile tissue
  - Slow potentials
    - Found in SA, AV node tissues

Fast Potential



Fast Potential

- Phase 0: Na^+ influx “fast sodium channels”
- Phase 1: K^+ efflux
- Phase 2: (Plateau) K^+ efflux
  - AND Ca^{++} influx
- Phase 3: K^+ efflux
- Phase 4: Resting Membrane Potential

Slow Potential

- Self-depolarizing
  - Responsible for automaticity
- Phase 4 depolarization
  - ‘slow sodium-calcium channels’
  - ‘leaky’ to sodium
- Phase 3 repolarization
  - K^+ efflux

Cardiac Pacemaker Dominance

- Intrinsic firing rates:
  - SA = 60 – 100
  - AV = 45 – 60
  - Purkinje = 15 - 45

Cardiac Pacemakers

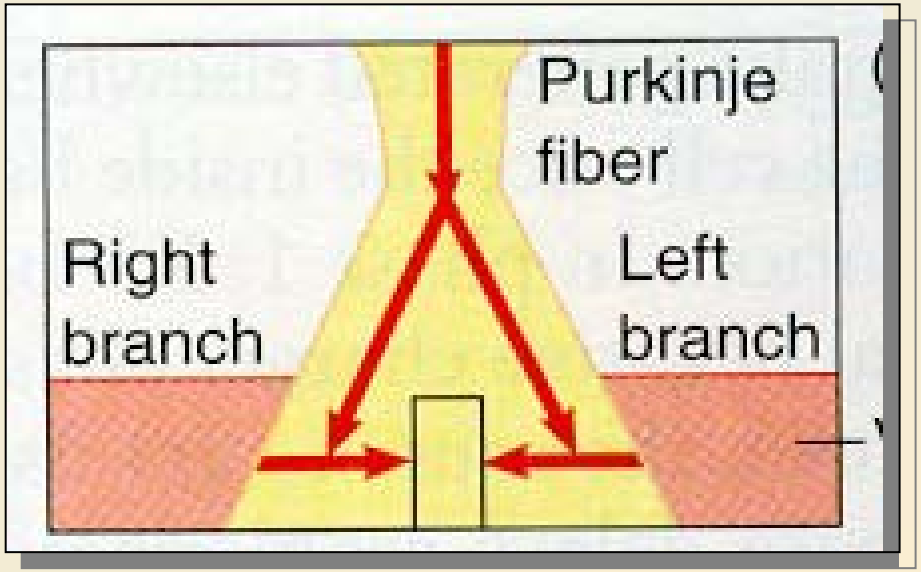
- SA is primary
  - Faster depolarization rate
    - Faster Ca^{++} 'leak'
- Others are 'backups'
  - Graduated depolarization rate
    - Graduated Ca^{++} leak rate

Dysrhythmia Generation

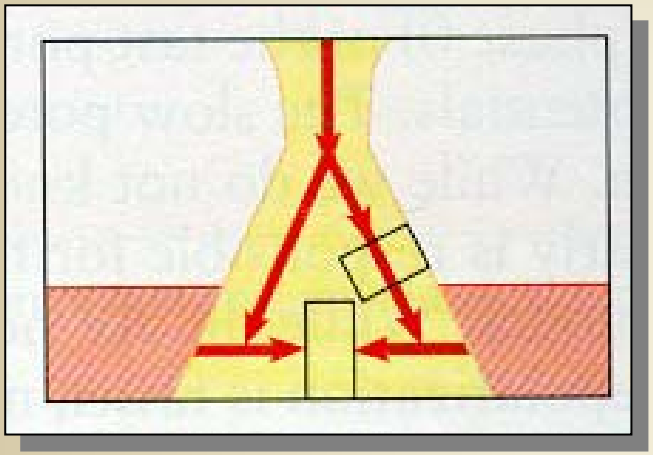
- Abnormal genesis
  - Imbalance of ANS stimuli
  - Pathologic phase 4 depolarization
    - Ectopic foci

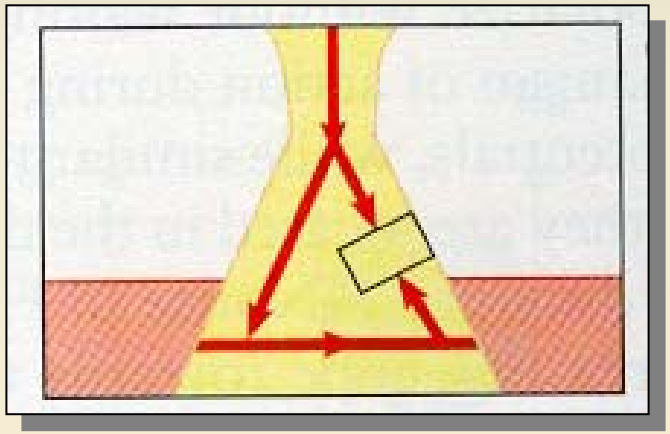
Dysrhythmia Generation

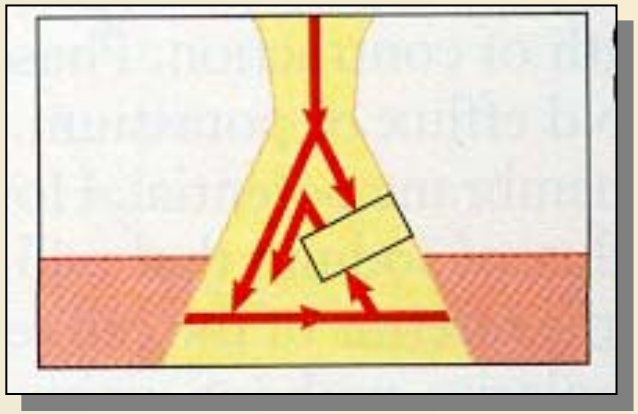
- Abnormal conduction
- Analogies:
  - One way valve
  - Buggies stuck in muddy roads



Reentrant Circuits







Warning!

- All antidysrhythmics have arrythmogenic properties
- In other words, they all can CAUSE dysrhythmias too!

AHA Recommendation Classifications

- Describes weight of supporting evidence NOT mechanism
- Class I
- Class IIa
- Class IIb
- Indeterminant
- Class III

- View AHA definitions

Vaughn-Williams Classification

- Class 1
  - Ia
  - Ib
  - Ic
- Class II
- Class III
- Class IV
- Misc

- Description of mechanism NOT evidence

Class I: Sodium Channel Blockers

- Decrease Na^+ movement in phases 0 and 4
- Decreases rate of propagation (conduction) via tissue with fast potential (Purkinje)
  - Ignores those with slow potential (SA/AV)
- Indications: ventricular dysrhythmias

Class Ia Agents

- Slow conduction through ventricles
- Decrease repolarization rate
  - Widen QRS and QT intervals
    - ***May promote Torsades des Pointes!***

- PDQ:
  - procainamide (Pronestyl®)
  - disopyramide (Norpace®)
  - qunidine
  - (Quinidex®)

Class Ib Agents

- Slow conduction through ventricles
- Increase rate of repolarization
- Reduce automaticity
  - Effective for ectopic foci
- May have other uses

- LTMD:
  - lidocaine (Xylocaine®)
  - tocainide (Tonocard®)
  - mexiletine (Mexitil®)
  - phenytoin (Dilantin®)

Class Ic Agents

- Slow conduction through ventricles, atria & conduction system
- Decrease repolarization rate
- Decrease contractility
- Rare last chance drug

- flecainide (Tambocor®)
- propafenone (Rythmol®)

Class II: Beta Blockers

- $Beta_1$ receptors in heart attached to Ca^{++} channels
  - Gradual Ca^{++} influx responsible for automaticity
- $Beta_1$ blockade decreases Ca^{++} influx
  - Effects similar to Class IV (Ca^{++} channel blockers)
- Limited # approved for tachycardias

Class II: Beta Blockers

- propranolol (Inderal®)
- acebutolol (Sectral®)
- esmolol (Brevibloc®)

Class III: Potassium Channel Blockers

- Decreases K^+ efflux during repolarization
- Prolongs repolarization
- Extends effective refractory period
- Prototype: bretyllium tosylate (Bretylol®)
  - Initial norepi discharge may cause temporary hypertension/tachycardia
  - Subsequent norepi depletion may cause hypotension

Class IV: Calcium Channel Blockers

- Similar effect as ß blockers
- Decrease SA/AV automaticity
- Decrease AV conductivity
- Useful in breaking reentrant circuit
- Prime side effect: hypotension & bradycardia

- verapamil (Calan®)
- diltiazem (Cardizem®)

- Note: nifedipine doesn't work on heart

Misc. Agents

- adenosine (Adenocard®)
  - Decreases Ca^{++} influx & increases K^{+} efflux via 2nd messenger pathway
    - Hyperpolarization of membrane
    - Decreased conduction velocity via slow potentials
    - No effect on fast potentials
- Profound side effects possible (but short-lived)

Misc. Agents

- Cardiac Glycocides
- digoxin (Lanoxin®)
  - Inhibits NaKATP pump
  - Increases intracellular Ca^{++}
    - via Na^{+}-Ca^{++} exchange pump
  - Increases contractility
  - Decreases AV conduction velocity

Pharmacology

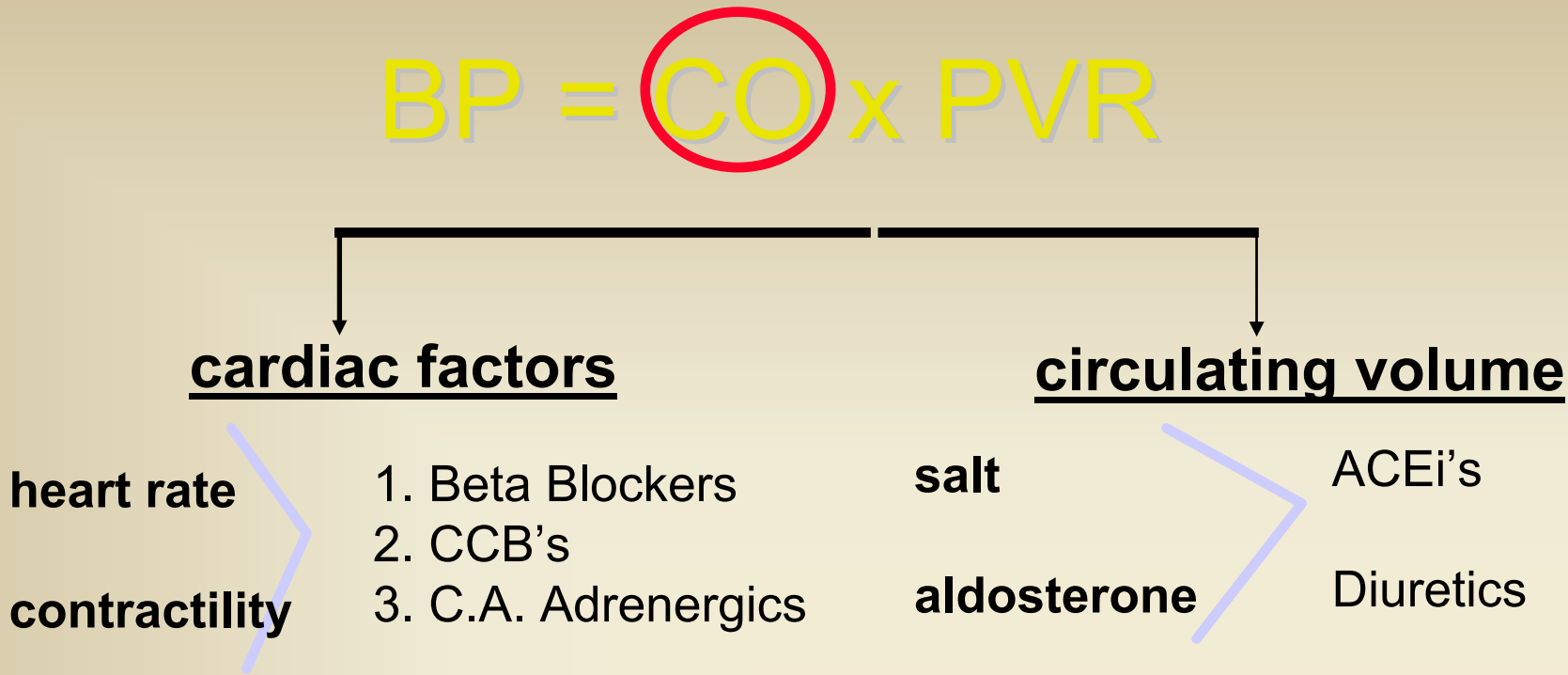
Antihypertensives

Antihypertensive Classes

- diuretics
- beta blockers
- angiotensin-converting enzyme (ACE) inhibitors
- calcium channel blockers
- vasodilators

Blood Pressure = CO X PVR

- Cardiac Output = SV x HR
- PVR = Afterload

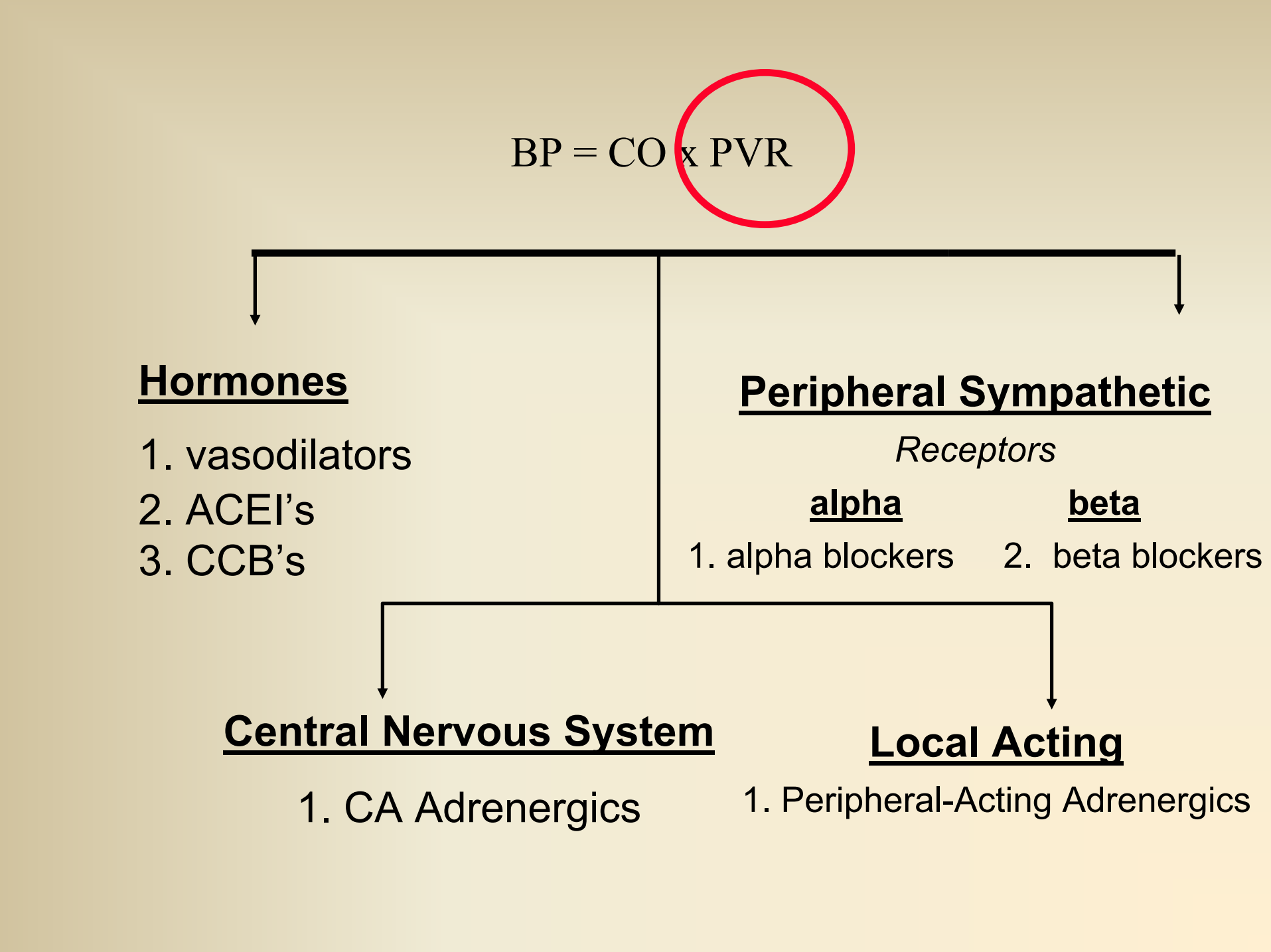


Key:

CCB = calcium channel blockers

CA Adrenergics = central-acting adrenergics

ACEi's = angiotensin-converting enzyme inhibitors


BP = CO x PVR
Hormones
1. vasodilators
2. ACEI's
3. CCB's
Peripheral Sympathetic
Receptors
alpha
beta
1. alpha blockers
2. beta blockers
Central Nervous System
1. CA Adrenergics
Local Acting
1. Peripheral-Acting Adrenergics

Alpha$_1$ Blockers

Stimulate alpha$_1$ receptors -> hypertension

Block alpha$_1$ receptors -> hypotension

- doxazosin (Cardura®)
- prazosin (Minipress®)
- terazosin (Hytrin®)

Central Acting Adrenergics

- Stimulate alpha$_2$ receptors
  - inhibit alpha$_1$ stimulation
    - hypotension

- clonidine (Catapress®)
- methyldopa (Aldomet®)

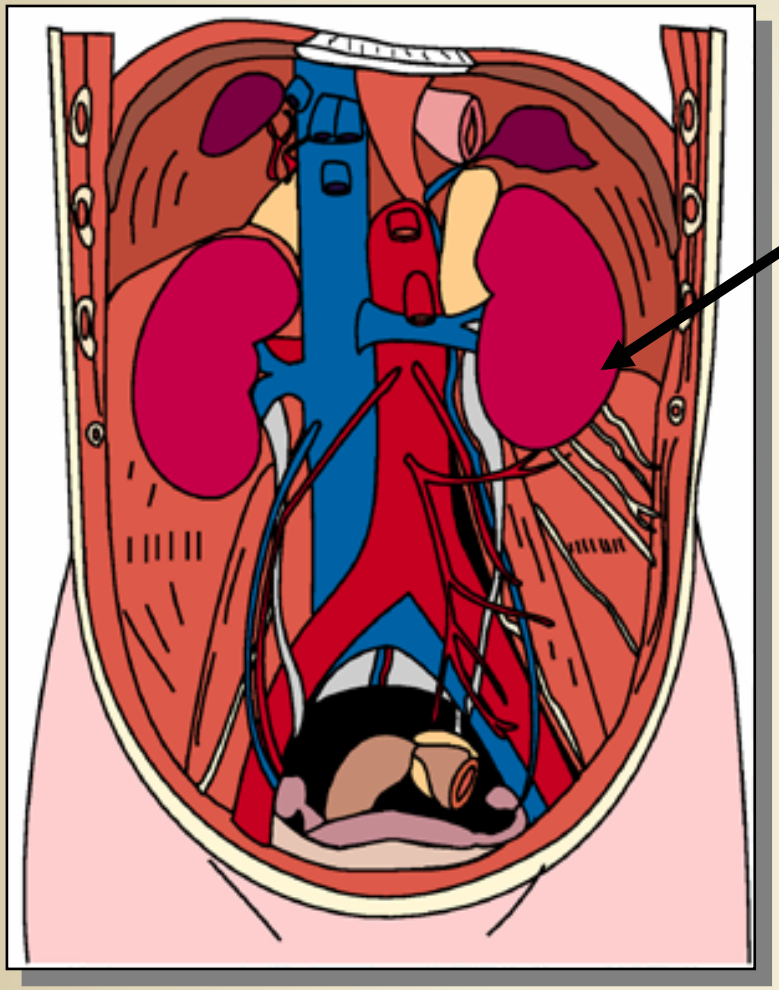
Peripheral Acting Adrenergics

- reserpine (Serpalan®)
- inhibits the release of NE
- diminishes NE stores
- leads to hypotension
- Prominent side effect of depression
  - also diminishes seratonin

Adrenergic Side Effects

- Common
  - dry mouth, drowsiness, sedation & constipation
  - orthostatic hypotension
- Less common
  - headache, sleep disturbances, nausea, rash & palpitations

ACE Inhibitors



RAAS

Angiotensin I

↓

ACE

↓

Angiotensin II

↓

1. potent vasoconstrictor
   - increases BP
2. stimulates Aldosterone
   - Na^+ & H_2O reabsorbtion

Renin-Angiotensin Aldosterone System

- Angiotensin II = vasoconstrictor
- Constricts blood vessels & increases BP
- Increases SVR or afterload
- ACE-I blocks these effects decreasing SVR & afterload

ACE Inhibitors

- Aldosterone secreted from adrenal glands cause sodium & water reabsorption
- Increase blood volume
- Increase preload
- ACE-I blocks this and decreases preload

Angiotensin Converting Enzyme Inhibitors

- captopril (Capoten®)
- enalapril (Vasotec®)
- lisinopril (Prinivil® & Zestril®)
- quinapril (Accupril®)
- ramipril (Altace®)
- benazepril (Lotensin®)
- fosinopril (Monopril®)

Calcium Channel Blockers

- Used for:
  - Angina
  - Tachycardias
  - Hypertension

CCB Action

- diltiazem & verapamil
  - decrease automaticity & conduction in SA & AV nodes
  - decrease myocardial contractility
  - decreased smooth muscle tone
  - decreased PVR
- nifedipine
  - decreased smooth muscle tone
  - decreased PVR

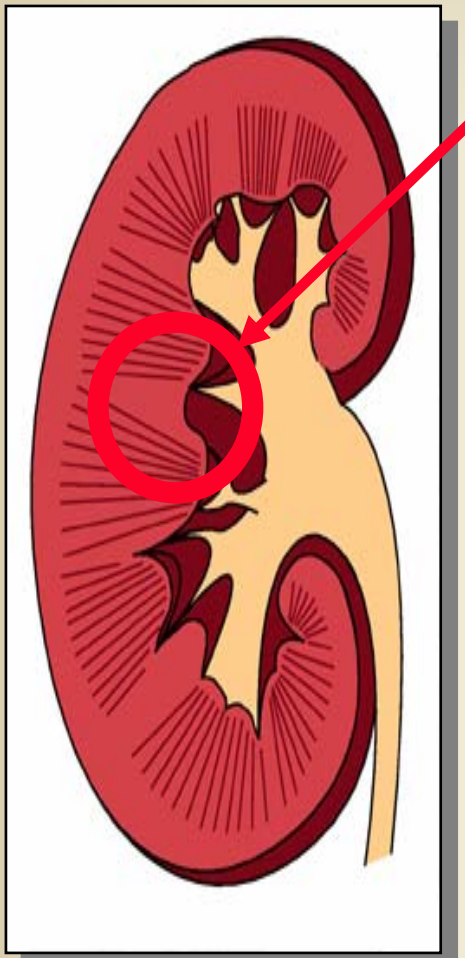
Side Effects of CCBs

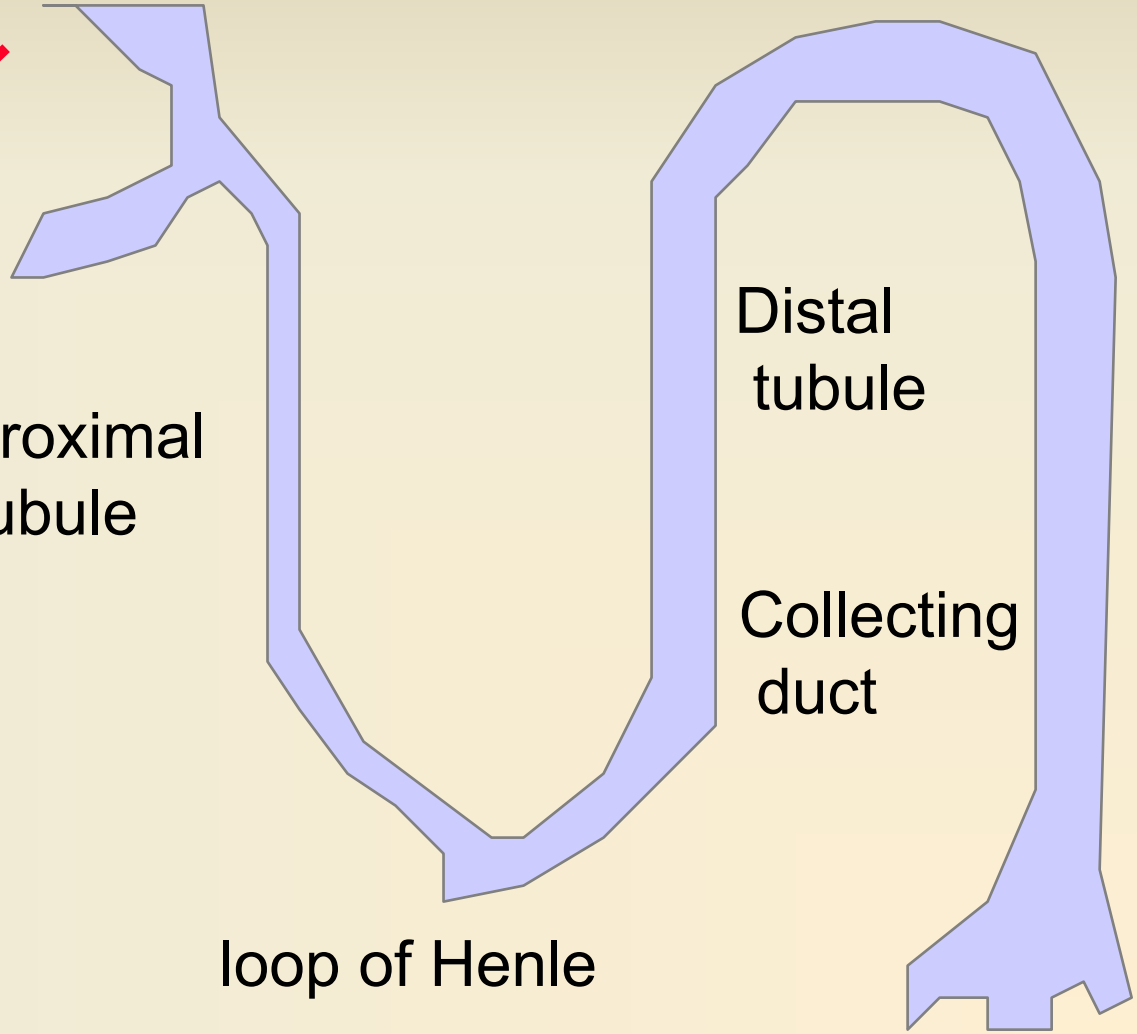
- Cardiovascular
  - hypotension, palpitations & tachycardia
- Gastrointestinal
  - constipation & nausea
- Other
  - rash, flushing & peripheral edema

Calcium Channel Blockers

- diltiazem (Cardizem®)
- verapamil (Calan®, Isoptin®)
- nifedipine (Procardia®, Adalat®)

Diuretic Site of Action





Mechanism

- Water follows Na^+
- 20-25% of all Na^+ is reabsorbed into the blood stream in the loop of Henle
- 5-10% in distal tubule & 3% in collecting ducts
- If it can not be absorbed it is excreted with the urine
- ⇓ Blood volume = ⇓ preload !

Side Effects of Diuretics

- electrolyte losses [Na^+ & K^+]
- fluid losses [dehydration]
- myalgia
- N/V/D
- dizziness
- hyperglycemia

Diuretics

- Thiazides:
  - chlorothiazide (Diuril®) & hydrochlorothiazide (HCTZ®, HydroDIURIL®)
- Loop Diuretics
  - furosemide (Lasix®), bumetanide (Bumex®)
- Potassium Sparing Diuretics
  - spironolactone (Aldactone®)

Mechanism of Vasodilators

- Directly relaxes arteriole smooth muscle
- Decrease SVR = decrease afterload

Side Effects of Vasodilators

- hydralazine (Apresoline®)
  - Reflex tachycardia
- sodium nitroprusside (Nipride®)
  - Cyanide toxicity in renal failure
  - CNS toxicity = agitation, hallucinations, etc.

Vasodilators

- diazoxide [Hyperstat®]
- hydralazine [Apresoline®]
- minoxidil [Loniten®]
- sodium Nitroprusside [Nipride®]

Pharmacology

Drugs Affecting Hemostasis

Hemostasis

- Reproduce figure 11-9, page 359 Sherwood

Coagulation Cascade

- Reproduce following components of cascade:
  - Prothrombin -> thrombin
    - Fibrinogen -> fibrin
  - Plasminogen -> plasmin

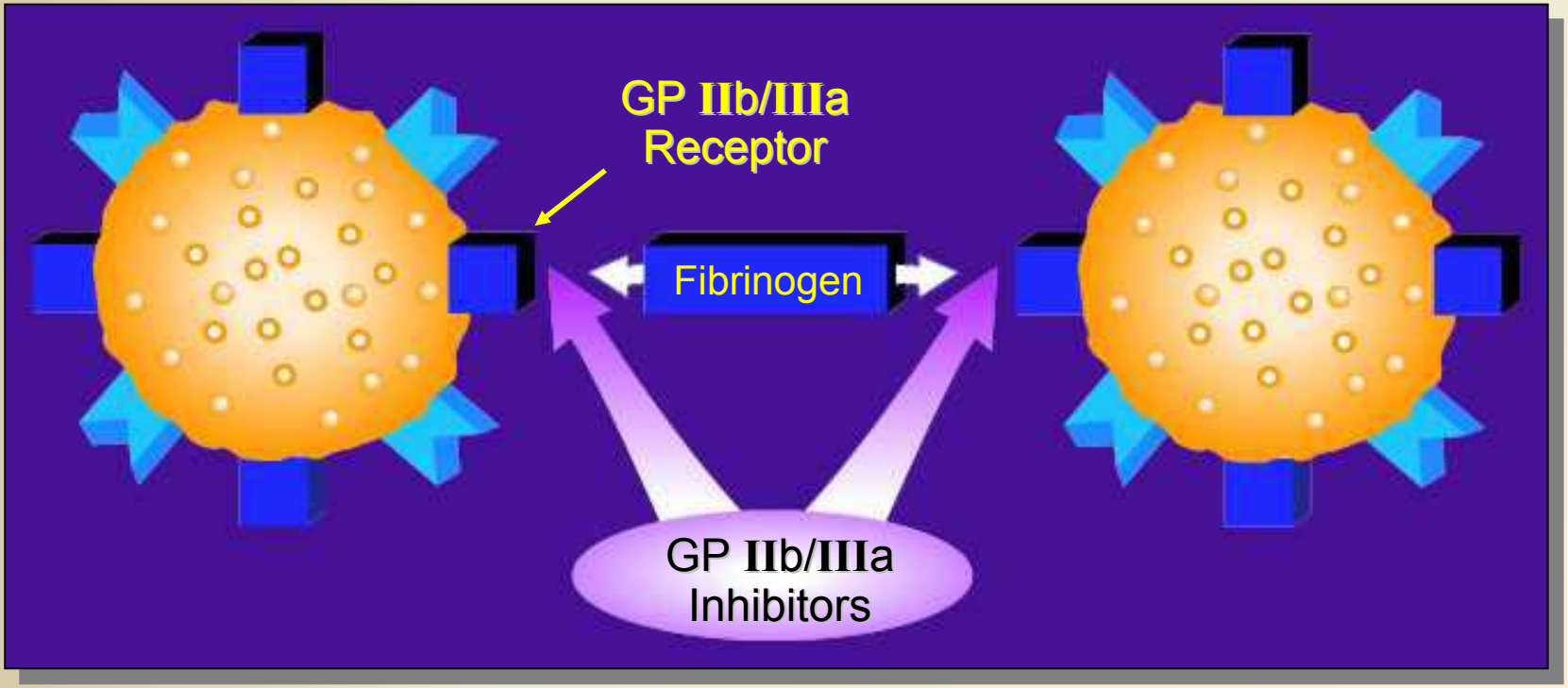
Platelet Inhibitors

- Inhibit the aggregation of platelets
- Indicated in progressing MI, TIA/CVA
- Side Effects: uncontrolled bleeding
- No effect on existing thrombi

Aspirin

- Inhibits COX
  - Arachidonic acid (COX) -> TXA2 (⇓ aggregation)

GP IIB/IIIA Inhibitors



GP IIB/IIIA Inhibitors

- abciximab (ReoPro®)
- eptifibitide (Integrilin®)
- tirofiban (Aggrastat®)

Anticoagulants

- Interrupt clotting cascade at various points
  - No effect on platelets
- Heparin & LMW Heparin (Lovenox®)
- warfarin (Coumadin®)

Heparin

- Endogenous
  - Released from mast cells/basophils
- Binds with *antithrombin III*
- Antithrombin III binds with and inactivates excess thrombin to regionalize clotting activity.
  - Most thrombin (80-95%) captured in fibrin mesh.
- Antithrombin-heparin complex 1000X as effective as antithrombin III alone

Heparin

- Measured in Units, not milligrams
- Indications:
  - MI, PE, DVT, ischemic CVA
- Antidote for heparin OD: protamine.
  - MOA: heparin is strongly negatively charged. Protamine is strongly positively charged.

warfarin (Coumadin®)

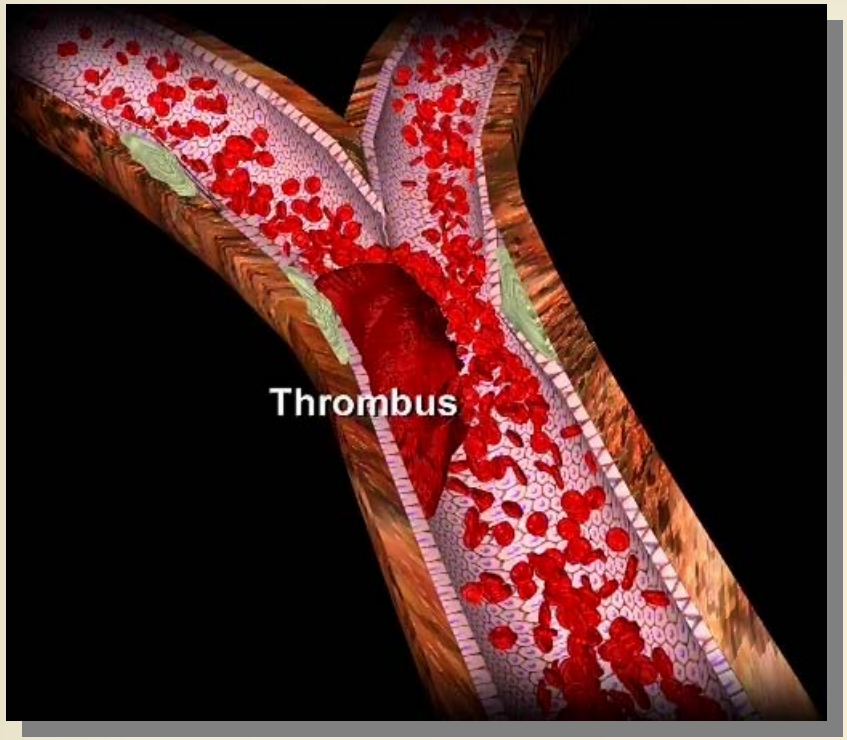
- Factors II, VII, IX and X all vitamin K dependent enzymes
- Warfarin competes with vitamin K in the synthesis of these enzymes.
- Depletes the reserves of clotting factors.
- Delayed onset (~12 hours) due to existing factors

Thrombolytics

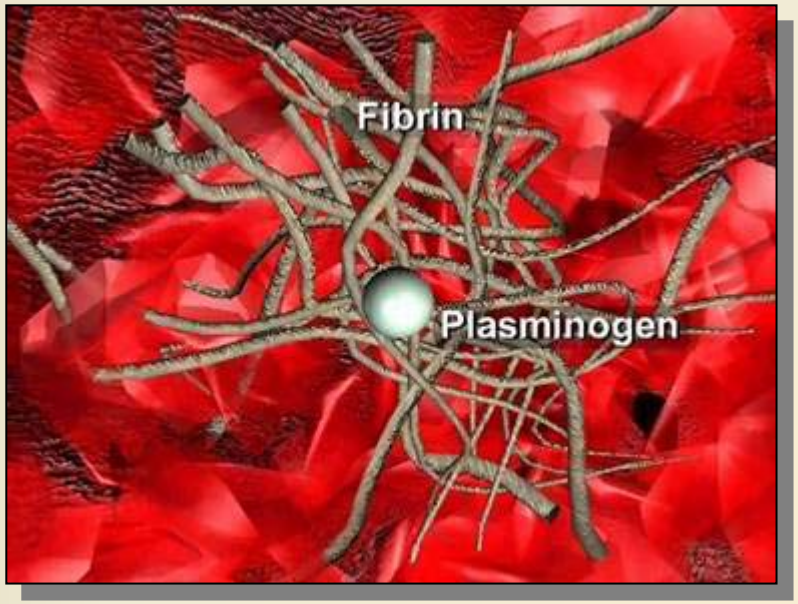
- Directly break up clots
  - Promote natural thrombolysis
- Enhance activation of plasminogen
- 'Time is Muscle'

- streptokinase (Streptase®)
- alteplase (tPA®, Activase®)
- anistreplase (Eminase®)
- reteplase (Retevase®)
- tenecteplase (TNKase®)

Occlusion Mechanism



tPA Mechanism



Cholesterol Metabolism

- Cholesterol important component in membranes and as hormone precursor
- Synthesized in liver
  - Hydroxymethylglutaryl coenzyme A reductase
  - (*HMG CoA reductase*) dependant
- Stored in tissues for latter use
- Insoluble in plasma (a type of lipid)
  - Must have transport mechanism

Lipoproteins

- Lipids are surrounded by protein coat to 'hide' hydrophobic fatty core.
- Lipoproteins described by density
  - VLDL, LDL, IDL, HDL, VHDL
- LDL contain most cholesterol in body
  - Transport cholesterol from liver to tissues for use ("Bad")
- HDL move cholesterol back to liver
  - "Good" b/c remove cholesterol from circulation

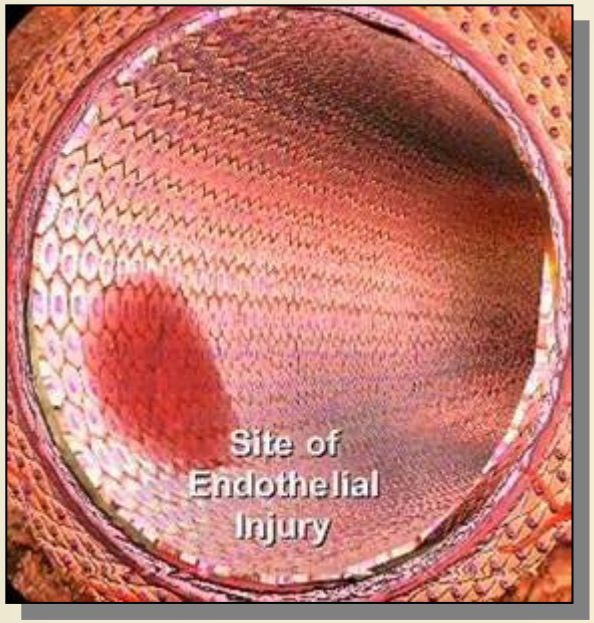
Why We Fear Cholesterol

- Risk of CAD linked to LDL levels
- LDLs are deposited under endothelial surface and oxidized where they:
  - Attracts monocytes -> macrophages
  - Macrophages engulf oxidized LDL
    - Vacuolation into 'foam cells'
  - Foam cells protrude against intimal lining
    - Eventually a tough cap is formed
  - Vascular diameter & blood flow decreased

Why We Fear Cholesterol

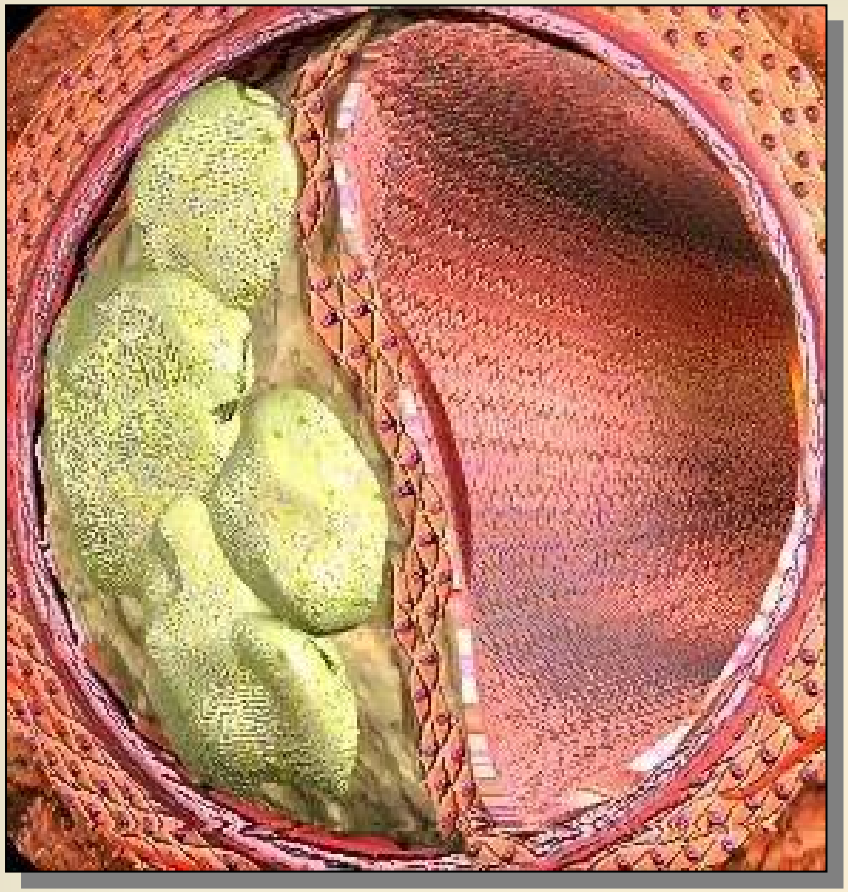
- Plaque cap can rupture
- Collagen exposed
- Clotting cascade activated
- Platelet adhesion
- Thrombus formation
- Embolus formation possible
- Occlusion causes ischemia

Lipid Deposition

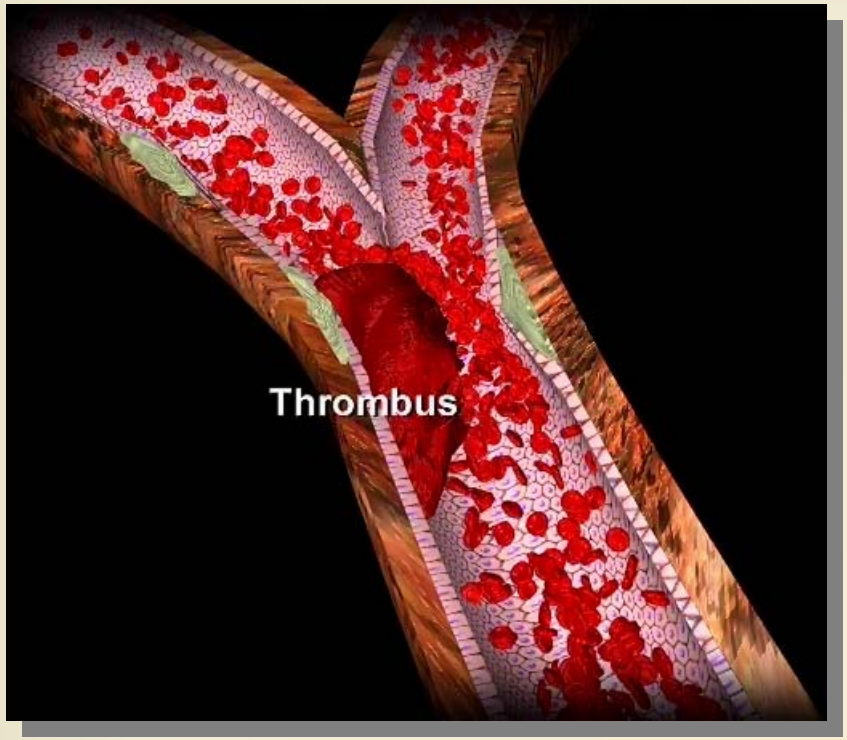


Thrombus Formation

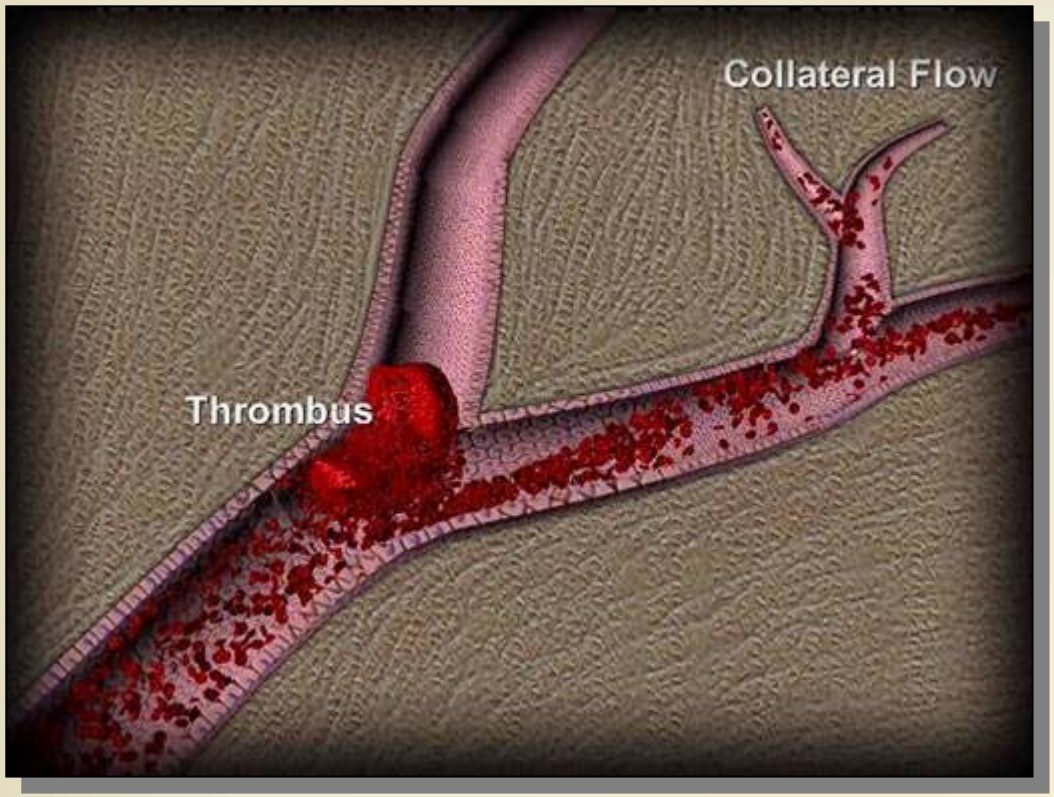
Platelet Adhesion



Embolus Formation



Occlusion Causes Infarction



Antihyperlipidemic Agents

- Goal: Decrease LDL
  - Inhibition of LDL synthesis
  - Increase LDL receptors in liver
- Target: < 200 mg/dl
- *Statins* are HMG CoA reductase inhibitors

- lovastatin (Mevacor®)
- pravastatin (Pravachol®)
- simvastatin (Zocor®)
- atorvastatin (Lipitor®)